LSE THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

wellcome trust

# EXECUTIVE SUMMARY FOR
# THE NEW LANDSCAPE OF NEGLECTED DISEASE DRUG DEVELOPMENT


Pharmacetical R&D Policy Project

Dr Mary Moran (Director), Anne-Laure Ropars, Dr Javier Guzman,
Dr Jose Diaz and Christopher Garrison

# EXECUTIVE SUMMARY FOR THE NEW LANDSCAPE OF NEGLECTED DISEASE DRUG DEVELOPMENT

Pharmacetical R&D Policy Project

Dr Mary Moran, Director

Anne-Laure Ropars

Dr Javier Guzman

Dr Jose Diaz

Christopher Garrison

September 2005

## Pharmaceutical R&D Policy Project

LSE Health and Social Care
Houghton Street
London WC2A 2AE

Tel: +44 (0)20 7852 3615
+44 (0)20 7852 3690

Email: j.guzman@lse.ac.uk
m.moran@lse.ac.uk
j.r.diaz@lse.ac.uk

## For further copies please contact:

Publications Department
The Wellcome Trust

Tel: +44 (0)20 7611 8651
Email: publishing@wellcome.ac.uk

Published by The Wellcome Trust
September 2005

This report was prepared by the London School of Economics and Political Science through a project funded by the Wellcome Trust. The views expressed are those of the authors and do not necessarily reflect Wellcome Trust policy.

# CONTENTS



# ACKNOWLEDGEMENTS

We would like to thank the many people who have so kindly given of their time and expertise in the course of discussions and consultations contributing to this project. The final report could not have been prepared without the very valuable input that was received from a wide range of constituencies including independent experts in public health and tropical diseases, and the staff of the Public-Private Partnerships and pharmaceutical and biotechnology companies concerned. The report has benefited greatly from their feedback and comments.

The PRPP gratefully acknowledges the tremendous support and assistance of the funders of the project, the Wellcome Trust; and the host of the project, the London School of Economics and Political Science. We also warmly thank the members of the project Steering Committee – Sir John Sulston, Sir Michael Rawlins, Professor Win Gutteridge and Professor Alistair McGuire.

## Foreword

The Pharmaceutical R&D Policy Project's fundamental aim is to improve health outcomes for developing country neglected disease patients by increasing the quality and number of drug treatments available to meet their needs (we do not examine vaccines or diagnostics). Within this broad framework, we focus specifically on policies and incentives that Western governments could implement to achieve this aim.

We have taken a strongly empirical approach, covering known neglected disease drug Research & Development (R&D) from 1975 to end 2004. All findings and conclusions are based on a review of existing knowledge, supported by original research and interviews with stakeholders involved in the development and use of new drugs. Strenuous efforts have been made to check primary sources and to verify our data with the relevant groups.

# THE NEW LANDSCAPE OF NEGLECTED DISEASE DRUG RESEARCH AND DEVELOPMENT

## Current perceptions of neglected disease drug development are missing the mark

Current policy thinking around neglected disease drug development is rooted in a set of shared understandings that have become accepted over the past decade, and which are largely based on the pre-2000 R&D landscape for these diseases.

One of these understandings is that only 13 new drugs have been developed for neglected tropical diseases since 1975[1], with the main problem being that these diseases are simply non-commercial for companies to invest in. Another is that, although Public-Private Partnerships (PPPs) for drug development have started, they are inexperienced and it is too early to judge their viability. A third common view is that the real experience and capability in drug development lies with multinational pharmaceutical companies, who must therefore be brought back into the neglected disease field if we are to achieve success.

The logical outcome of these collective beliefs is to focus on new policies to commercialise neglected disease markets on a scale to match large company needs (billions not millions). For example, we note the Commission for Africa's recent statement that we need to increase neglected disease R&D by 'giving large pharmaceutical firms incentives to investigate the diseases that affect Africa, instead of focusing on the diseases of rich countries'.[2]

However, our research shows that the pre-2000 picture no longer holds true and that the landscape of neglected disease drug development has changed dramatically over the past five years. At the end of 2004, over 60 neglected disease drug development projects were in progress (see Figure 1), including two new drugs in registration stage and 18 new products in clinical trials, half of which are already at Phase III. Assuming there were sufficient funding, at standard attrition rates this would be expected to deliver eight to nine drugs within the next five years, even if no further projects were commenced after the end of 2004.[I] (Some additional independent small company and early academic activity has not yet been fully captured, and would be expected to increase this figure even further.)

I DNDi, the TB Alliance and MMV expected yield based on the respective attrition rates proposed by each organisation; other projects (industry and other PPPs) based on Tufts figures (DiMasi J, Hansen R, Grabowski H (2003) The price of innovation: new estimates of drug development costs; Journal of Health Economics 22: 151-185).

This renewed activity – at a level unheard of in the past two decades – has occurred in the absence of significant new government incentives and largely without public intervention; and is not explained by our current understanding of why companies do or do not conduct neglected disease R&D. Failure to recognise and understand these changes, and what motivates them, may lead to misdirected and wasteful public policies or, at worst, to the collapse of a valuable and active source of new neglected disease drugs.

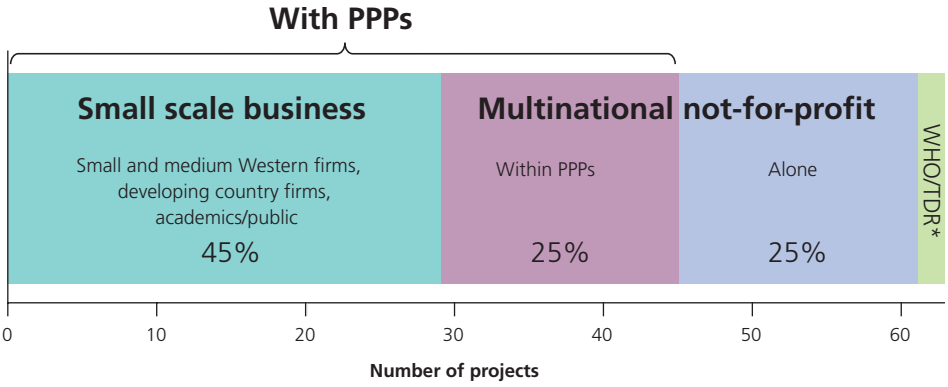
In order to provide policy-makers with the information they need to improve neglected disease drug R&D policies, this report focuses on three areas. Section 1 analyses current neglected disease activity, identifying the main R&D approaches and the motivations behind them. Section 2 analyses the performance of the different approaches in terms of health outcomes and efficiency, including their ability to deliver useful new drugs. Section 3 builds on this information to develop a set of novel policy recommendations aimed at supporting the most effective and efficient approaches to neglected disease drug R&D.

## The new R&D landscape: identifying the main contributors and understanding their motivations

Neglected disease R&D activity in the post-2000 landscape falls into two categories. The first is multinational pharmaceutical company activity conducted on a not-for-profit basis; the second is small-scale activity conducted on a fully-paid or commercial basis by small companies (including both Western and developing country firms) and academics or public institutions. The majority of this activity, by both small and large players, is conducted under the umbrella of Public-Private Partnerships, who are now responsible for three-quarters of all identified neglected disease drug development projects (see Figure 1 below).

Multinationals, small companies and PPPs are discussed in detail. However, less attention is given to the motivations and operations of developing country firms and public/academic groups, since the focus of this report is on industry policies or incentives that could be implemented by Western governments or donors.

**Figure 1. The drug R&D landscape for neglected diseases (Dec 2004): 63 active drug development projects (See Annexe 1)**

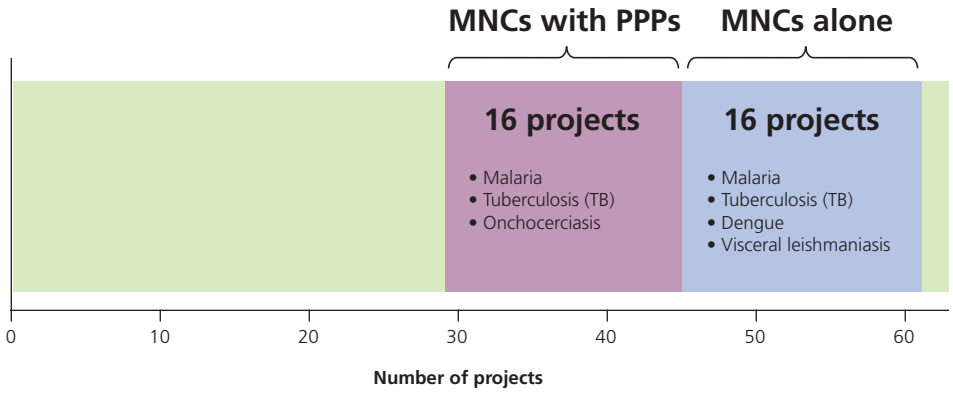



*Unable to verify details for three projects by the World Health Organisation Special Programme for Research and Training in Tropical Diseases (WHO/TDR)

### Multinational Pharmaceutical Companies

Multinational drug companies conduct around half of current neglected disease drug development activity (32 projects) either working with PPPs or working alone (albeit usually with a view to subsequent partnering). The bulk of this activity is accounted for by the four companies who have formal neglected disease divisions: GlaxoSmithKline, Novartis, AstraZeneca and Sanofi-Aventis; while four other companies have less formal neglected disease activity, conducting perhaps one or two projects each, and generally on a more serendipitous basis.

**Figure 2. Neglected disease drug R&D projects carried out by Multinational Pharmaceutical Companies (MNCs) (Dec 2004)**




In all cases, these companies are working on *a not-for-profit* basis – that is, they are not motivated by commercial returns in neglected disease markets and have agreed to provide the final products to poor patients in developing countries at not-for-profit prices. This approach is driven by longer-term business concerns, including managing reputational risk, addressing ethical issues, and strategic positioning in growing developing country commercial markets.

This renewed activity has been catalysed and facilitated by several deep-seated structural changes since 2000, with two developments being particularly noteworthy: a move by multinational companies to early-pipeline R&D, and the formation of new PPPs for drug development.

In the years prior to 2000, government R&D policies and incentives were largely premised on early public development of drug leads with multinational company involvement in *later-stage clinical development*, including large-scale developing country trials. This type of industry contribution is expensive, has high associated liability risks and is an area in which most Western-focused companies have little or no experience. Therefore most companies responded by pulling out of the neglected disease field altogether; or by restricting the number of their projects and focusing on less risky and less costly 'adaptive R&D' – for example, reformulations, re-registrations or new combinations of existing drugs. The results were in many cases poor, as demonstrated by the performance metrics outlined below.

By contrast, since 2000 most R&D-active multinational companies have moved to *early pipeline* R&D, including the formation of three new institutes dedicated solely to neglected disease drug discovery. Under this approach, companies develop promising new neglected disease leads and take these to the point of clinical development, at which time public partners are sought to fund further development and to assist with the complex and risky process of developing country clinical trials (some companies seek public partnering from even earlier stages). Working together, the company and the PPP partner can then trial, register and distribute the final drugs, with each providing skills and inputs in their area of comparative advantage. For instance, the public partner normally contributes developing country and neglected disease knowledge and skills, and assistance with developing country drug registration and implementation; while the company prepares and guides regulatory submissions and takes responsibility for manufacture and distribution (either themselves or via licensing to a generic manufacturer).

This approach relies heavily on – indeed is probably dependent on – the presence of public partners who can help companies take promising leads through to development and implementation. However, it is attractive to companies since it is significantly less costly to them; is more easily controlled and ring-fenced in terms of company investment; and does not leave firms to carry the high-liability risks associated with developing country trials, particularly in children and pregnant women.

Importantly, it also allows companies – whose direct R&D costs are now substantially subsidised by cash or in-kind public inputs – to offer the resulting drugs to developing country patients at not-for-profit prices (ie at, or close to, their cost of production). This *'no profit-no loss'* model, as one company calls it, has three key advantages:

- it provides a source of high-quality innovative drug leads;
- it uses public skills in their area of maximum comparative advantage (developing country clinical trials rather than drug design);
- it provides products to poor patients at not-for-profit prices.

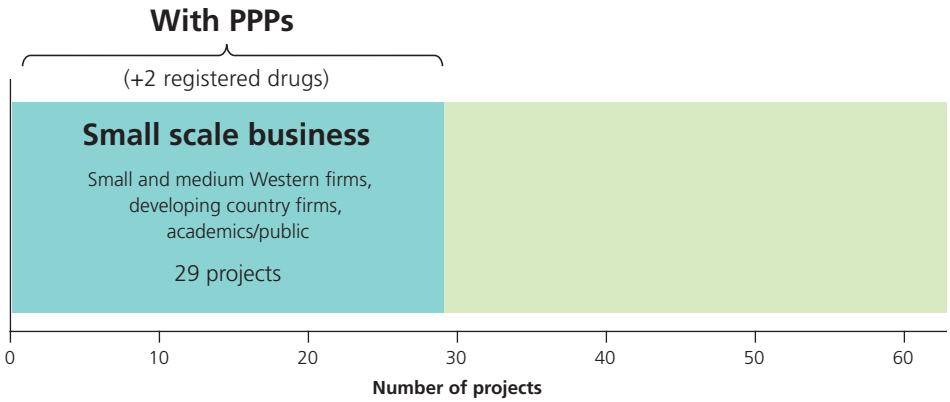
A number of other multinational companies do not conduct neglected disease R&D and say that no commercial incentives – unless ridiculously large, as one company put it – will make them re-enter the neglected disease field. These companies want to contribute, but in ways that do not require the more substantial commitment made by R&D-active companies.

Overall, a key problem of current public policy proposals is that they are built on the now-outdated beliefs outlined above, and are therefore poorly matched to these new approaches. Consequently, they seem likely to encourage companies away from their current approach to neglected disease R&D (high innovation early-pipeline activity; high public health input via partnering; and not-for-profit drug delivery to patients), and back into the pre-2000 model (high-risk, expensive late-stage industry activity; industry-alone R&D without structured public health input; and activity restricted by profit potential).

## Small companies [II]

Small companies now represent a substantial proportion of new neglected disease activity, with around half of all identified 60-plus R&D projects being conducted by PPPs with smaller commercial partners or academic drug developers (see Figure 3 below). PPP commercial contracts with small companies are now roughly equal in value to PPP contracts with multinational companies.

**Figure 3. Neglected disease drug R&D projects carried out under the small scale business model (Dec 2004)**




II Small company activity is discussed in this report only insofar as it is linked to a PPP. Examples of 'independent' neglected disease drug development initiatives by small firms were documented (eg by Sequella or Palumed), but will not be discussed here as a more extensive survey would need to be done to capture the entirety of this activity. We note however that the views and motivations of these companies, which we also interviewed, were the same as those within the subgroup discussed here.

Small firms involved in neglected disease R&D with PPPs are universally driven by commercial motivations ie by the expectation of shorter-term profit either in the neglected disease market itself or in a related Western market, and are highly unlikely to be in a position where altruistic, strategic or longer-term business considerations alone would offer a sufficient stimulus to conduct neglected disease R&D.

These small companies fall under three broad categories, depending on where their commercial interest lies:

Some small companies see neglected disease markets themselves as sufficiently attractive to warrant investment (particularly larger markets such as TB and malaria), and will pursue these even without public support. For example, small firms have recently developed or are currently developing new drugs for leishmaniasis and sleeping sickness and several products for malaria and TB.

A second – and potentially much larger – category is that of small firms who can use 'add-on' neglected disease R&D to support their primary Western commercial focus. For instance, these firms may use neglected disease R&D to expand their information on core commercial compounds, or to establish proof-of-concept for a technology that can then be transferred to commercial markets. However, unlike most multinational firms, these small companies require full PPP support to enable this 'add-on' neglected disease activity, including *full cost coverage* of the neglected disease R&D component, and substantial technical assistance in often unfamiliar neglected disease and developing country aspects. In the absence of such support and funding, many of these firms are unlikely to pursue an overlapping neglected disease indication and will return to an exclusive Western focus.

Finally, commercial Contract Research Organisations (CROs) increasingly see neglected disease R&D as an interesting niche sector, and are now involved on a commercial basis in one-third of current PPP projects. This involvement is again entirely reliant on the relevant PPP having sufficient funds to sign commercial contracts.

The commercial interest that drives small companies to engage in neglected disease R&D is more sustainable by nature than R&D driven by strategic or altruistic motivations. However, it remains largely unexploited. Most small companies continue to be deterred by the substantial barriers to entry that are characteristic of large, disseminated and unfamiliar developing country markets. Moreover, firms with a primary Western focus can have difficulty concluding financial agreements with cash-strapped PPPs, particularly if their intellectual property concerns are not adequately addressed. Current public R&D incentives are also poorly suited to small company needs: public assistance in minimising barriers to market entry is very limited, and inadequate public funding for PPPs continues to restrict business opportunities for all small firms.

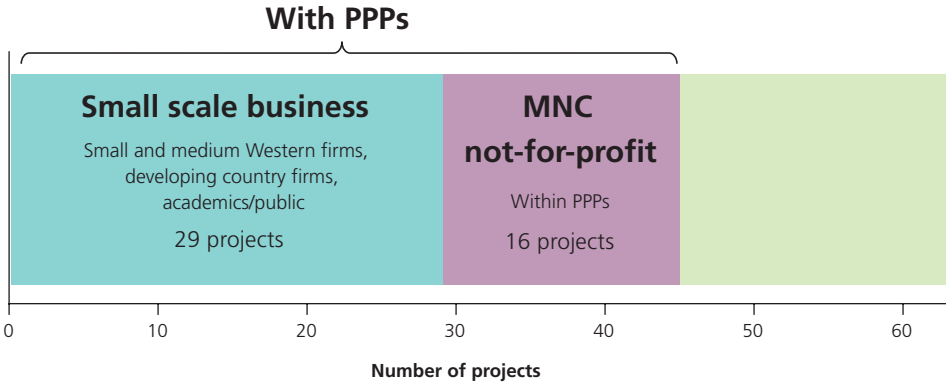
## Public-Private Partnerships (PPPs)

PPPs conduct three-quarters of all identified neglected disease drug development projects (see Figure 4 below), with their current portfolios expected to yield six to seven new neglected disease drugs within five years[III]. This activity is being conducted by the *four drug development PPPs* set up since 2000[IV] and by WHO/TDR. (WHO/TDR operates as a de facto PPP in the sense that it develops drugs through industry partnerships, however it has a very different modus operandi from the four formal PPP organisations.)

III see Footnote I above

IV We define PPPs as public-health driven not-for-profit organisations that drive neglected disease drug development in conjunction with industry groups. The four neglected disease drug development PPPs set up since 2000 are: Medicines for Malaria Venture (MMV), the TB Alliance, Drugs for Neglected Diseases initiative (DNDi), and the Institute for OneWorld Health (iOWH).

**Figure 4. Neglected disease drug R&D projects carried out by PPPs (Dec 2004)**




The central presence of PPPs in neglected disease drug development reflects their crucial role in facilitating multinational company involvement and their catalytic role in much small company activity, as noted above. It is this ability to catalyse and bring together private sector drug development activity with public sector health and neglected disease skills that is central to the superior performance metrics of the PPP model, as outlined below.

Appropriate public policies to support PPPs need to be based on a clear understanding of their functions and of the specific advantages of this model. In particular, PPPs do not conduct drug development themselves. Their main functions are to:

- integrate and co-ordinate multiple industry and academic/public partners and contractors along the drug development pipeline;
- allocate philanthropic and public funds to the right kinds of R&D projects from a public health perspective;
- manage neglected disease drug portfolios by various means including selection and termination of projects based on their relative merits.

By virtue of these functions and of their overall cost-efficiency (see performance metrics below), PPPs offer significant benefits to public funders by increasing the efficiency of government expenditure on R&D while, at the same time, decreasing government risk in choosing which projects to fund. Their integration, allocation and management roles also allow PPPs to stimulate alternative approaches to drug development. PPPs can develop compounds from many different sources, even if no industry partner is involved, for instance, leads from academia or shelved company compounds. Alternatively, by actively pairing up small Western companies with developing country manufacturers, PPPs can – and do – sustain a neglected disease drug development pipeline that can be far cheaper than the traditional commercial approach.

Nevertheless, despite these clear advantages, PPPs receive very little public (as opposed to philanthropic) support. The thirty OECD[v] members, with a collective GDP of nearly US $30 trillion per year[3], have contributed only US $43 million to drug development PPPs over the past five years (see Table 1), leaving these PPPs with a 2005 shortfall of around 40 per cent as of early 2005. There are also no public policies in place specifically to underwrite industry's current participation in PPPs or to encourage their increased future participation. This lack of public funding is a growing concern as PPP projects increasingly move into the expensive clinical stages.

Finally, we raise our doubts about the use of the term 'Public-Private Partnership'. As seen from the discussion above, many Public-Private Partnership projects for drug development have neither public funding nor private partners, and many fall outside any reasonable definition of partnership. We do not have a better term to offer, but suggest this is an area where more accurate nomenclature could help to dispel a number of mistaken beliefs.



v Organisation for Economic Co-operation and Development (OECD)

**Table 1. Breakdown of cumulative philanthropic and public funding to drug PPPs (as of April 2005, including forward-funding committed by that date)***

| Donor | Total funding (US $) | Per cent of total |
|---|---|---|
| **Philanthropic** | | |
| Bill and Melinda Gates Foundation | 158,757,717 | 58.9 |
| Médecins Sans Frontières (MSF) | 29,738,133 | 11.0 |
| Rockefeller Foundation | 20,300,000 | 7.5 |
| The Wellcome Trust | 2,827,504 | 1.1 |
| **Sub-total** | **211,623,354** | **78.5** |
| **Public** | | |
| US government | 16,000,000 | 5.9 |
| UK government | 10,909,468 | 4.1 |
| Netherlands government | 10,489,255 | 3.9 |
| Swiss government | 4,422,285 | 1.6 |
| European Commission | 1,554,150 | 0.6 |
| **Sub-total** | **43,585,077** | **16.2** |

* Excludes WHO/TDR

# PERFORMANCE METRICS

Increased neglected disease R&D is always welcome, but it is also important that this R&D is targeted to optimal health outcomes for developing country patients, and that it represents the most cost-efficient use of philanthropic and public funding (ie that patients see maximum health returns for every dollar spent). Therefore this section assesses the performance of differing approaches to neglected disease R&D (eg industry working alone, industry-public partnerships, public drug development) across a number of criteria:

- health value for developing country patients:
  - safety
  - efficacy
  - suitability
  - affordability
  - level of innovation
- efficiency of the drug development process:
  - capacity (ability to make drugs)
  - development times
  - cost and cost-efficiency

Outcomes against selected criteria are outlined overleaf.

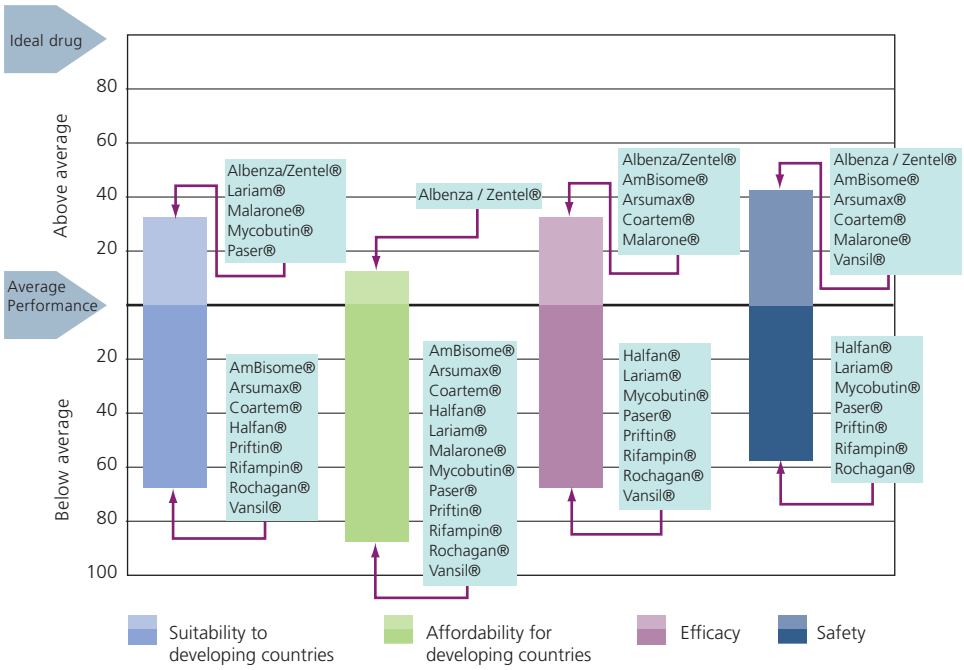
## Health outcomes

The most important overall metric is the health impact of the final product for the target developing country patients. Health value could only be measured for 21 completed projects[VI] ie projects that registered new drugs between 1975 and 2004 (other projects are still in the development stage). 13 of these completed projects were conducted by industry working alone, and eight under a partnered 'PPP' approach between industry and public health groups. There are, as yet, no registered drugs developed fully in the public sector that we are aware of.

The 'PPP' approach delivered the best health outcomes for developing country patients. Eight neglected-disease projects were conducted in public-private collaborations (public input from WHO/TDR and academics)[VII]. Three of the resulting products had a major impact on developing country health – Mectizan® (ivermectin), which halved the global burden of onchocerciasis between 1990 and 2000[4]; praziquantel, which has helped to control schistosomiasis in Brazil, the Mahgreb, the Middle East, China, and the Philippines[5]; and the WHO/TDR-assisted label extension of Coartem® tablets for paediatric use, which has delivered Africa its first safe, effective, suitable new anti-malarial for many years.

By contrast, 12 of the 13 drugs[VIII] developed by industry alone had a low *overall* health value for developing country patients, with only one product being widely accessible and useful in the developing world (Zentel®/albendazole). Overall, the single greatest obstacle to developing country use of these industry-developed drugs is poor performance against the affordability metric (see Figure 5 below). In many cases this stems from the choice of a lead compound that is unlikely ever to be affordable in a developing country setting because of the high cost of the active pharmaceutical ingredients or high formulation costs, resulting in treatment costs as high as thousands of dollars per patient. This can be due to inattention to Developing Country (DC) – relevant concerns, or because companies choose and design leads for overlapping Western commercial markets where safety and efficacy, rather than cost or ease of use, are the main drivers. For example, companies may target travellers' and military malaria, AIDS opportunistic infections, or the OECD market for TB or HIV-associated TB.

**Figure 5. Health value of industry-alone neglected disease drugs**
(Drugs are listed alphabetically within each category – no ranking is implied)




VI We note that Coartem® was registered twice, and therefore both registrations were considered as separate projects. (The second registration was a label extension to suit developing country needs five years after the initial registration).

VII These eight drugs were Artemotil®, Paluther®, Coartem® tablets paediatric label extension, Lapdap®, Biltricide®, Impavido®, Ornidyl® and Mectizan®.

VIII These 13 drugs were Zentel®, Lariam®, Malarone®, Mycobutin®, Paser®, AmBisome®, Arsumax®, Coartem® original registration for adults and children above 10kg in a four-dose (not six-dose) formulation, Halfan®, Priftin®, Rifampin®, Rochagan® and Vansil®.

## Level of innovation

Incremental innovation can offer marked benefits to patients. For instance, fixed-dose combinations of existing drugs can greatly improve ease of use and compliance; follow-on drugs in the same class may improve safety and efficacy; and paediatric formulations can make childhood treatments simpler and more reliable.

However, if we are to effectively manage health outcomes in the long-term then we must also overcome the growing problem of drug resistance in many neglected disease areas, including malaria, TB, leishmaniasis, and sleeping sickness. Overcoming resistance means not only simplifying and improving existing therapies, but also focussing urgently on 'breakthrough' innovation – that is, on the discovery and development of new compounds with a novel mechanism of action against parasites and microbes.

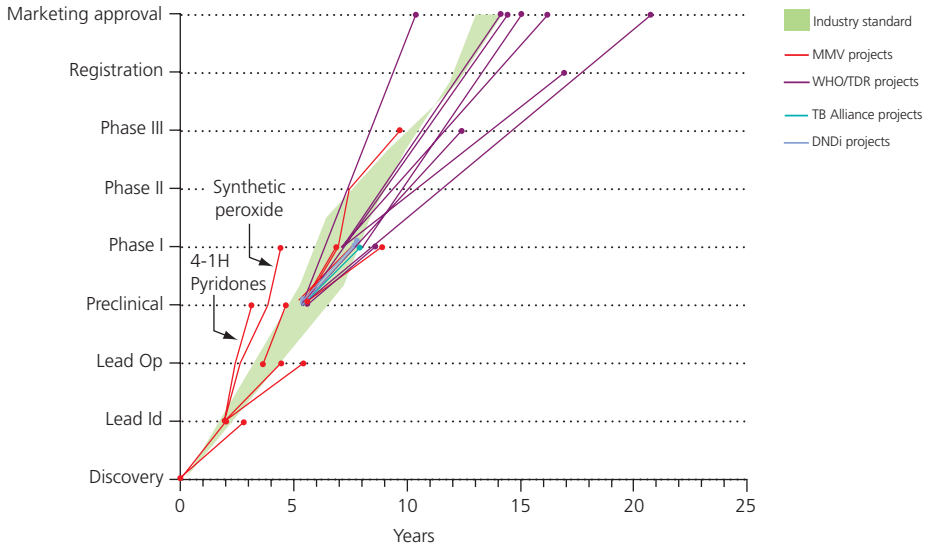
Measurement of the level of breakthrough innovation under each R&D approach shows that PPPs and current industry 'partnering' approaches (ie early stage industry projects with a view to public partnering for clinical trials) perform best. Nearly half of all PPP projects (49 per cent) and more than half of industry partnering projects (63 per cent) are in the breakthrough category, compared to only 8 per cent of drugs developed by industry working alone under the pre-2000 model. We note that these figures should not be directly compared, since the pre-2000 innovation figure is based on *registered* drugs while the post-2000 figures are for *ongoing projects* and will therefore have a different profile once attrition rates are factored in.

Nevertheless, irrespective of attrition rates, the key explanation for the much higher share of breakthrough innovation projects post-2000 is the recent major shift in industry neglected-disease R&D strategy discussed above. The serendipitous approach that characterised the past 25 years has given way to one that is specifically focused on high-innovation early stage discovery R&D. In the long-term, this approach can only deliver high-innovation products.

## Development trajectories

Although the level of innovation is important, it is equally critical that R&D projects move quickly to bring new drugs to patients who need them as early as possible. Time metrics show that most PPP drug development trajectories match or exceed industry standards. These are the Tufts Timeline (based on data on 68 approved new biopharmaceuticals and small molecule New Chemical Entities)[6] and the Parexel/MMV Timeline (based on Parexel's sourcebook).[7] In particular, projects conducted by PPPs are significantly faster than public-alone drug development (see Figures 6,7 and 8 below) and generally exceed industry trajectories for neglected-disease new chemical entities (although the latter are too few in number to draw significant conclusions). The exception is WHO/TDR, whose timelines fall below those of formal PPPs, possibly reflecting its very different approach to partnered drug development.

**Figure 6. PPPs timelines***




* No timelines could be plotted for iOWH projects

**Figure 7. Industry timelines**

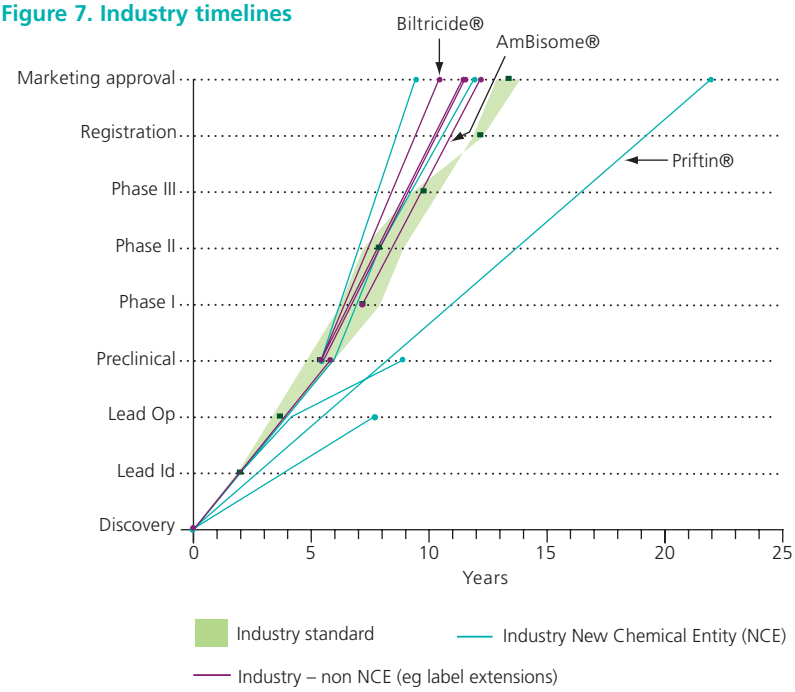
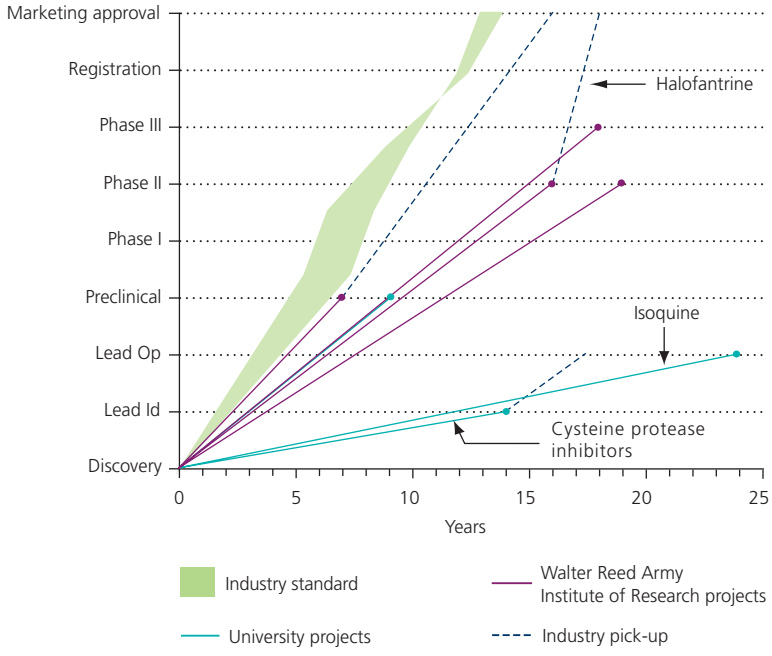



**Figure 8. Public timelines**




## Cost-efficiency

The overall cost-efficiency of PPPs is superior to other approaches – partly, but not only, due to their ability to leverage substantial in-kind inputs from partners and by the exclusion of costs of capital from the PPP 'push' model. The total cost of collective PPP drug development activity from 2000 to 2004 (excluding WHO/TDR, for which numbers were not available) was US $112 million, including cost of failure, for more than 40 projects (one of these in registration and ten in clinical trials, including four at Phase III). Per-project costs were also remarkably low in most of the cases we examined (although confidentiality agreements prevent us from disclosing the majority of these). For example, Medicines for Malaria Venture's synthetic peroxide project has moved from discovery, through lead identification, lead optimisation and pre-clinical, and into Phase I trials at a total cost of US $11.5 million (see Table 2 below). Costs of completed projects will, of course, be higher.

**Table 2. R&D costings for selected PPP projects**

| Project Name | Type of project | R&D costed | Indication | Cost * US $million | Unquantified pro bono input |
|---|---|---|---|---|---|
| **ACTUAL COSTS** | | | | | |
| FAS II | New chemical entity | **Lead identification** | Malaria | **2.7** | Nil |
| PFT inhibitors | New chemical entity | **Lead identification** | Malaria | **2.2** | Some expert advice and data from BMS |
| Pyronaridine-artesunate | Fixed dose combination | **Preclinical (+3 months Phase I)** | Malaria | **5.3** | Shin Poong's input (formulation chemistry) |
| PA-824 | New chemical entity | **Preclinical** | Tuberculosis | **4.5** | Expert advice from ex-company employee |
| Synthetic peroxide | New chemical entity | **Discovery Lead identification Lead optimisation Preclinical (+6 months Phase I)** | Malaria | **11.5** | Expert advice from Roche |
| **PROJECTED COSTS** | | | | | |
| Pyronaridine-artesunate | Fixed dose combination | **From preclinical up to registration** | Malaria | **15-20** | |
| PA-824 | New chemical entity | **From preclinical up to end of phase III** | Tuberculosis | **86** | |

* We have used internal budgets, and added pro-rata'd indirect scientific costs.

The industry cost of developing a new chemical entity for Western markets is substantially higher, being estimated by the Tufts Institute at US $802 million per drug including cost of failure and cost of capital, and at US $403 million for out-of-pocket R&D costs per drug (including cost of failure)[6]. While indicative, these numbers do not hold fully for neglected-disease drug development, which some companies suggested at interview would be substantially cheaper (for example, around US $50 million to take a new compound from discovery through to the start of clinical trials). However, even using these lower estimates, PPP figures to date suggest that they can still be expected to perform significantly better on cost-efficiency and cost.

## Overall performance

Public-private drug development collaborations performed better on most metrics than either industry working alone or public groups working alone. In other words, and perhaps unsurprisingly when we consider the matter more closely, drug development for neglected diseases is optimised by combining industry drug development expertise with public neglected disease expertise. Identified correlates of success common to most successful projects (and absent from poorly performing projects) were:

- a focus on neglected disease drug development for developing countries over all other considerations
- industry involvement from an early stage
- public involvement from an early stage
- appropriate use of the respective skills of the public and industry partners
- management and scientific staff with industrial drug-making experience
- adequate funding
- larger portfolios

We emphasise that the superior outcomes seen under the partnered approach do not reflect the capacity of the individual players, but rather the inherent ability of different R&D approaches to deliver optimal outcomes. Thus, a company working in a public partnership may be able to deliver a better outcome than the same company working alone, since the public 'safety net' (both financial and technical) can allow the company to expand to higher-risk but more innovative R&D and to include higher-risk but equally needy patient groups into the clinical drug development process.

# POLICY RECOMMENDATIONS

Good policy making is as much about designing the right levers as it is about providing funds.

Effective (and cost-effective) policies will closely match the activity and needs of different players, as outlined above. Attempting to motivate multinational companies who have limited interest or skills in neglected disease R&D is likely to be less effective than motivating firms (large and small) whose interests, business models and/or skills already predispose them to neglected disease activity. Likewise, it seems best to offer financial incentives to companies with financial motives and non-financial incentives to those with other drivers. Good policies will also support approaches that deliver optimal public health outcomes and maximum cost-efficiency on public investment, and they will be carefully tailored to align stakeholder behaviour with desired public outcomes, including incentivising and rewarding best-practice activities.

Our analysis of the different R&D approaches – industry, PPPs, and public sector – has been conducted with these principles firmly in mind. The resulting recommendations have been specifically tailored to match the identified motivations, needs, strengths and weaknesses of the respective players, and to align their R&D practices with the correlates of success. On the basis of our findings, we recommend that policy-makers support two main approaches:

- **Publicly-funded R&D**. If neglected disease R&D is to be supported by public funds, then policy-makers should choose the cheapest and most effective approach. Our findings suggest this is best achieved by combining industry drug development skills with public neglected disease skills through Public-Private Partnerships, including partnerships with interested or potentially interested multinational companies and with small firms who could derive commercial benefit from neglected disease R&D;
- **Small company market-driven activity**. By this, we mean activity driven by existing market demand for neglected disease products, which is a sustainable mechanism, as opposed to 'markets' created by public subsidies, since these are no more sustainable than other publicly funded approaches. We suggest examining the feasibility of complementing PPP activity with small company market-driven activity (we specify small companies, since their commercial scale is better suited to neglected disease markets than that of multinational companies), but suggest that some issues specific to small companies may need closer examination before any policy decisions can be made. In particular, small firms are often less experienced in end-pipeline drug development, and may need additional attention to ensure developing country health outcomes are protected and optimised.

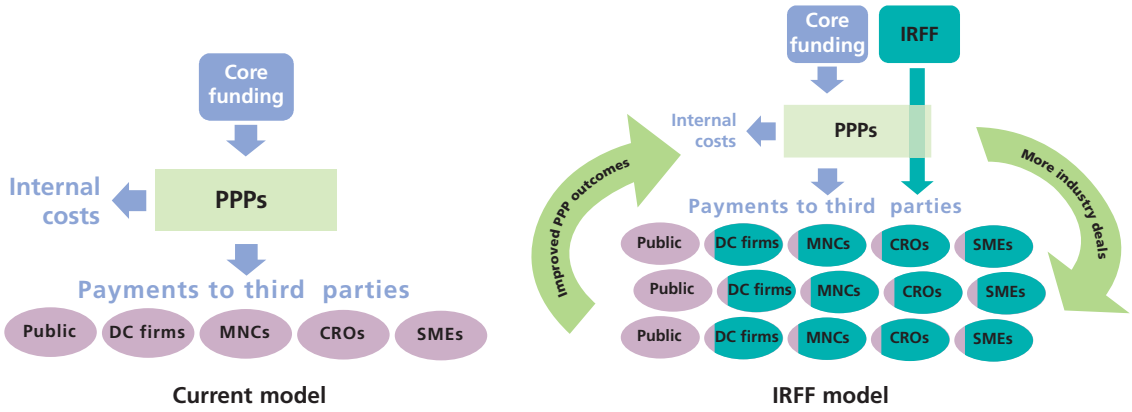
It is also clear that current and future neglected disease activity, by PPPs or others, inevitably means that we will see more projects entering large-scale clinical trials. This will require not only substantially increased funding but also far greater attention to streamlining, integrating and facilitating the clinical trial, registration and implementation processes for new neglected disease drugs. This is now a pressing priority, although outside the remit of this report.

## Recommendation 1

Create a new public fund, the Industry R&D Facilitation Fund (IRFF). The IRFF will be additional to the core funding PPPs currently receive from public and philanthropic groups, and will underwrite the cost of PPP industry contracts as follows:

- PPPs continue to pay industry – large and small – for neglected disease R&D as they do now;
- PPPs receive a long-term commitment from the IRFF (eg five years with yearly reviews) to partially finance their industry payments (perhaps 80 per cent of total industry payments) as their portfolio moves along (see Figure 9 below);
- the replenished PPPs are able to conclude more deals with big and small companies, supporting both the no profit-no loss model of multinationals and the commercial approach of small companies.

**Figure 9. PPP cash flows under the current model and under the IRFF model***




*MNCs: Multinational Pharmaceutical Companies, SMEs: Small and Medium-sized Enterprises, CROs: Contract Research Organisations, DC: Developing Country

The IRFF aligns the incentives of all players with the correlates of success, and creates a virtuous cycle: it encourages and facilitates increased industry participation in partnered neglected disease activity (the most cost-efficient and effective approach from the public health point of view), while the introduction of additional industry skills and compounds in turn further improves PPP portfolios and performance. Donor funds are directly targeted at project payments and are spent as and when needed as projects move forward, while risk is decreased as the IRFF allows donors to fund a consolidated global neglected disease portfolio across all PPPs. Finally, the IRFF will yield rapid outcomes, as it supports a fully operating model that is due to deliver six to seven drugs in the next five years.

Anticipated cost: US $1.3 to US $1.9 billion over 10 years (less than US $200 million/year across all donors).

## Recommendation 2

Provide additional supports for PPPs. Examples include:

- providing additional funding to allow PPPs to license promising compounds from small companies or to offer 'start-up' funding to small companies with compounds of shared neglected disease and commercial interest;
- a shared services platform across PPPs, eg for legal services, CRO services, human resources services; help with negotiating deals with big and small pharmaceutical firms;
- reductions on PPP patent-filing and maintenance fees relating to products for developing country neglected disease use.

## Recommendation 3

Examine the feasibility of stimulating small company market-driven neglected disease activity, including measures to foster optimal health outcomes from this activity.

A sample of measures suggested for further study include proposals to:

- minimise barriers to developing country market entry, for example, by creating a formal neglected disease 'package', which would at a minimum include regulatory assistance and fee relief, pre-qualification of new drugs developed, expedited listing on WHO's Essential Drugs List, and approval for purchase by international procurement bodies. (In practice, measures to simplify market entry would benefit all groups conducting neglected disease R&D.)
- provide small firms with assistance in dealing with developing country regulatory and health authorities, in locating suitable developing country trial sites and in locating suitable developing country manufacturing and distribution partners;
- give impetus and support to a double bottom-line equity fund[IX] to finance small start-up companies working in the neglected disease area, or with neglected disease-relevant technologies;
- consolidate disseminated developing country markets by providing expanded or additional centralised purchasing mechanisms for new neglected disease drugs;
- protect public health outcomes when small companies work independently to develop new drugs, for example, by providing a neglected disease scientific network to assist these firms and early and ongoing assistance in designing developing country trials.

## Recommendation 4

Sell (or possibly auction off) the right to partial fast-track registration of one additional commercial drug per year (Fast Track Option – FTO), with the resulting funds being dedicated to neglected disease drug development.

Existing fast track legislation is a formal package of regulatory measures that allows drugs to be developed and registered more quickly, and therefore reach patients sooner. Fast track includes two types of time-saving measures: regulatory efficiencies (eg scientific advice, regular meetings with the regulatory agency) and shortcuts in the R&D process (eg smaller trials). A limited number of drugs are currently eligible for fast track, with most commercial drugs being excluded. For instance, many 'priority' drugs, defined by the FDA as drugs offering a clear benefit to US patients over existing therapies, are currently ineligible for fast track registration.

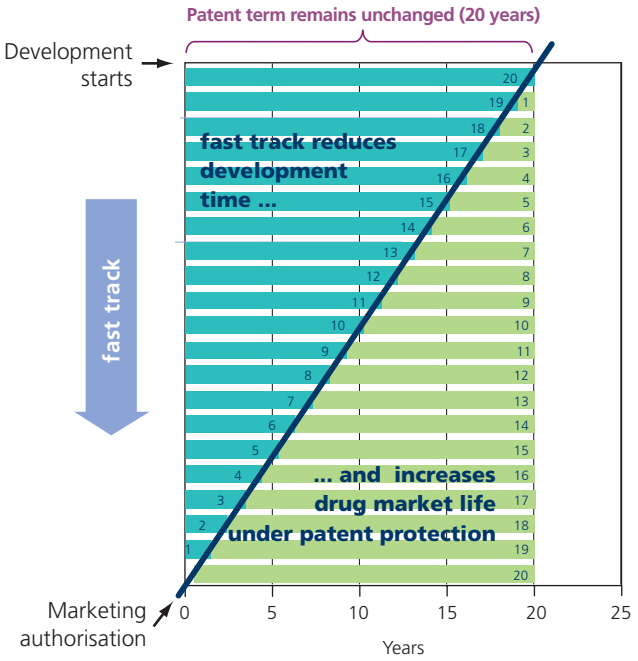
The FTO proposal set out here would allow a company to acquire the right to partially fast track a currently ineligible commercial drug (including priority drugs). The right is partial since it would include fast track regulatory efficiencies but would **categorically exclude R&D shortcuts**. A company who acquired an FTO for one of its drugs in development would get the benefit of reaching the market (and profits) before its competitors, with potential time savings of up to 2.5 years. The discounted value of an FTO (allowing for risk that the drug fails before reaching registration) would be in the order of US $0.27 billion – US $0.52 billion[X] in additional after-tax returns on a blockbuster drug that reached the market two years early. Real value if the drug was successful would be US $0.5-0.75 billion.

By selling an FTO yearly, the public sector can capture and share the value of this efficiency, with the potential to raise well over US $100 million per year to fund neglected disease R&D. FTOs have the additional benefits of bringing a number of commercial drugs to Western patients sooner (and would not delay the entry of generics, as transferable patent extensions would – see Figure 10 below), and allowing increased public scrutiny of the drug development process (a specific feature of fast track review).

IX Double bottom-line funds seek both financial and social returns on their investment (hence 'double' bottom line), accepting sub-market private returns in exchange for achieving desired public-good outcomes. In our proposal, the fund would seek public health returns in the form of new drugs being developed for neglected diseases as well as private returns.

X Estimated as present value of future returns at time of purchasing the FTO, assuming the drug is five years away from registration. The use of the FTO for that drug is assumed to lead to a launch two years early.

**Figure 10. The fast track mechanism**




**Fast track is an efficiency gain: it increases the patent-protected market life of the drug, but does NOT increase patent term and hence does NOT delay entry of generics.**

## Recommendation 5

Improve the flow of information among interested stakeholders by:

- providing a central clearing-house for information on targets or compounds relevant to neglected disease drug development, sources of neglected disease funding, and services and skills provided by public partners.

## Recommendation 6

Offer a significant public-relations prize for the multinational company that has contributed the most to neglected disease drug development each year.

## Recommendation 7

Create a structured platform to centralise and co-ordinate inputs from pharmaceutical companies who want to contribute to neglected disease R&D but may not want to conduct such R&D themselves, for example, for contributions of:

- expertise, eg medicinal chemistry advice, members for Expert Scientific Advisory Committees (ESACs);
- in-kind platform services, eg regulatory dossier preparation, trial data management, project management, portfolio and financial planning;
- high-throughput screening of company compound libraries.

## Recommendation 8

Increase support for public research linked to drug development, by:

- ensuring that public basic research funding includes minimum funding targets for translation research to convert basic research findings into new drug leads;
- providing subsidised industrial medicinal chemistry advice to public groups or academics.

# ANNEXE

## Annexe 1. List of active neglected disease drug R&D projects as of end 2004 (grouped as PPPs and industry projects)

### Annexe 1a. Neglected disease R&D landscape – PPPs (December 2004)

| | Compound | PPP | Partners | Indication | Current stage |
|---|---|---|---|---|---|
| 1 | Artemisone | MMV | Bayer HealthCare, Hong Kong Uni | Malaria | Clinical (Phase II) |
| 2 | DHF reductase | MMV | BIOTEC (Thailand), LSHTM, Monash Uni | Malaria | Lead identification |
| 3 | Peptide deformylase-PDF | MMV | GSK | Malaria | Discovery |
| 4 | 4(1H)-pyridones | MMV | GSK | Malaria | Preclinical |
| 5 | 4(1H)-pyridones back-ups- | MMV | GSK | Malaria | Lead optimisation |
| 6 | Isoquine | MMV | GSK, Liverpool Uni | Malaria | Preclinical |
| 7 | FAB 1 | MMV | GSK | Malaria | Discovery |
| 8 | Falcipains | MMV | GSK, UCSF | Malaria | Lead identification |
| 9 | Chlorproguanil dapsone/ artesunate (CDA) | MMV | GSK, WHO/TDR, Liverpool Uni | Malaria | Clinical (Phase II) |
| 10 | DB-289 Malaria | MMV | Immtech, North Carolina Uni | Malaria | Clinical (Phase I – II) |
| 11 | New dicationic molecules | MMV | North Carolina Uni, STI | Malaria | Lead optimisation |
| 12 | FAS II | MMV | Texas A&M Uni, Albert Einstein College of Med, Jacobus | Malaria | Lead identification |
| 13 | Artemether-lumefantrine (Paediatric Coartem®) | MMV | Novartis | Malaria | Clinical (Phase I) |
| 14 | Novel tetracycline | MMV | Paratek | Malaria | Lead identification |
| 15 | Synthetic peroxide (Oz) | MMV | Ranbaxy, Nebraska Uni, Monash Uni, STI, Roche | Malaria | Clinical (Phase I) |
| 16 | Synthetic peroxide (Oz) Next Generation | MMV | Nebraska Uni, Monash Uni, STI | Malaria | Lead identification |
| 17 | Pyronaridine/artesunate | MMV | Uni Iowa, Shin Poong, WHO/TDR | Malaria | Clinical (Phase I) |
| 18 | Dihydroartemisinin-piperaquine (Artekin®) | MMV | Sigma Tau, Chongqing Holley, Holleykin Pharma, Oxford Uni | Malaria | Clinical (Phase I-III) |
| 19 | GAPDH | MMV | STI | Malaria | Discovery |
| 20 | Manzamine A | MMV | Mississippi Uni | Malaria | Lead optimisation |
| 21 | 8-aminoquinolone | MMV | Mississippi Uni | Malaria | Preclinical |
| 22 | Pf-PFT inhibitors | MMV | Washington Uni, Yale Uni | Malaria | Lead optimisation |
| 23 | IV Artesunate | MMV | WRAIR | Malaria | Preclinical |
| 24 | Gatifloxacin | WHO/TDR | Lupin, EC Consortium, Thammasat University, TBRC (India) | Tuberculosis | Clinical (Phase III) |
| 25 | Eflornithine – oral | WHO/TDR | MSF | HAT* | Clinical (Phase III) |

*Continued*

| | Compound | PPP | Partners | Indication | Current stage |
|---|---|---|---|---|---|
| 26 | Berenil | WHO/TDR | Unknown | HAT* | Preclinical |
| 27 | Posaconazole for Chagas | WHO/TDR | Unknown | Chagas disease | Preclinical |
| 28 | Rectal artesunate | WHO/TDR | Unknown | Malaria | Registration/ Phase IV |
| 29 | Moxidectin | WHO/TDR | Wyeth | Onchocerciasis | Clinical (Phase II) |
| 30 | Isocitrate lyase inhibitors | TB Alliance | GSK | Tuberculosis | Lead identification |
| 31 | Enoyl-ACP-reductase inhibitors | TB Alliance | GSK | Tuberculosis | Lead identification |
| 32 | Pleuromutilins | TB Alliance | GSK | Tuberculosis | Lead optimisation |
| 33 | Focused Screening | TB Alliance | GSK | Tuberculosis | Discovery |
| 34 | Quinolones | TB Alliance | KRICT, Yonsei Uni | Tuberculosis | Lead identification |
| 35 | Macrolides | TB Alliance | Illinois Uni | Tuberculosis | Lead identification |
| 36 | Nitroimidazole analogs | TB Alliance | Novartis, NIAID | Tuberculosis | Lead optimisation |
| 37 | Nitroimidazole PA-824 | TB Alliance | Fully subcontracted to CROs; RTI | Tuberculosis | Preclinical |
| 38 | Carboxylates | TB Alliance | Wellesley College | Tuberculosis | Lead identification |
| 39 | HTS on whole cell trypanosomes | DNDi | Harvard Uni (ICCB) | HAT* | Discovery |
| 40 | Trypanothione reductase inhibitors | DNDi | Harvard Uni (ICCB), Dundee Uni | HAT* | Discovery |
| 41 | Protein farnesyl-transferase inhibitors | DNDi | Washington Uni | HAT* | Discovery |
| 42 | Paromomycin for VL in Africa | DNDi | Leishmania East Africa Platform (LEAP), WHO/TDR | Visceral leishmaniasis | Clinical (Phase III) |
| 43 | Artesunate-mefloquine FDC | DNDi | Far Manguinhos, Mahidol Uni, Universiti Sains (Malaysia), Oxford Uni,MSF, WHO/TDR | Malaria | Clinical (Phase III) |
| 44 | Artesunate-amodiaquine FDC | DNDi | Sanofi-Aventis, Centre Nationale de Recherche et de Formation sur le Paludismo (Burkina Faso) Tropival/ Bordeaux 2 Uni (France), Universititi Sains (Malaysia), Oxford Uni, MSF, WHO/TDR | Malaria | Clinical (Phase III) |
| 45 | New technology for artemisinin production | iOWH | Amyris Biotechnologies, UCSF Keasling lab | Malaria | Discovery |
| 46 | CRA 3316/K777 | iOWH | NIH, Celera Genomics, UCSF | Chagas disease | Preclinical |
| 47 | Paromomycin for VL for India | iOWH | WHO/TDR, IDA, Indian Pharmaceutical Manufacturer | Visceral leishmaniasis | Registration |

* Human African Trypanosomiasis

## Annex 1b. Neglected Disease R&D landscape – MNCs working alone (December 2004)

| | MNC | Compound | Indication | Current Stage |
|---|---|---|---|---|
| 1 | Sanofi-Aventis | Thiazolium | Malaria | Lead optimisation |
| 2 | Sanofi-Aventis | Choline uptake inhibitors | Malaria | Lead optimisation |
| 3 | Sanofi-Aventis | Ferroquine (SSR 97193) | Malaria | Phase I |
| 4 | Sanofi-Aventis | Trioxaquine | Malaria | Lead optimisation |
| 5 | Sanofi-Aventis | Intrarectal quinine | Malaria | Phase III |
| 6 | Novartis | PDF inhibitors | Tuberculosis | Lead optimisation |
| 7 | Novartis | NS3 helicase | Dengue** | Discovery |
| 8 | Novartis | NS5 polymerase | Dengue** | Discovery |
| 9 | Novartis | NS3 protease | Dengue** | Discovery |
| 10 | AstraZeneca | DNA synthesis inhibitors | Tuberculosis | Lead identification |
| 11 | AstraZeneca | Methyl erythritol pathway inhibitors | Tuberculosis | Lead identification |
| 12 | AstraZeneca | Unspecified Dev project | Tuberculosis | Lead optimisation |
| 13 | Pfizer | U 100480 | Tuberculosis | Preclinical? |
| 14 | Pfizer | Zythromicin+chloroquine | Malaria | Phase III |
| 15 | J&J | R207910 (diarylquinolone) | Tuberculosis | Phase I |
| 16 | GSK | Sitamaquine (WR6026) oral | Visceral Leishmaniasis | Phase III |

** There is no PPP for Dengue

# REFERENCES


1 Pecoul B, Chirac P, Trouiller P, Pinel J (1999). Access to essential drugs in poor countries: a lost battle? JAMA; 281: 361-67

2 Commission for Africa (2005) Final report: 'Our common interest'. March 2005. Available at www.commissionforafrica.org/english/report/thereport/english/11-03-05_cr_report.pdf

3 OECD (2005) Main economic indicators. June 2005

4 Shibuya K, Bernard C et al (2005); Global burden of onchocerciasis in the year 2000: Summary of methods and data sources. Epidemiology and Burden for Disease (EBD), Global Programme on Evidence for Health Policy (GPE), World Health Organization. Draft 17 Jun 2005

5 Chitsulo L, Loverde P, Engels D (2004) Schistosomiasis. Nat Rev Microbiol. Jan; 2(1):12-3

6 Di Masi J A, Hansen R W, Grabowski H G (2003) The price of innovation: new estimates of drug development costs. Journal of Health Economics 22: 151-185

7 MMV (2003) MMV Business Plan 2003-2007, Appendix 9.2 'Estimated phase durations'




Design: **LSE Design Unit** (www.lse.ac.uk/designunit)